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RECENT ADVANCES IN CAPSULE TECHNOLOGY: A REVIEW

Rupali N. Rathod*, Lokesh G. Barade, Harshal L. Tare

TSPM's, Trimurti Institute of Pharmacy Jalgaon, Maharashtra, India

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For Correspondence:

Rupali N. Rathod

TSPM's, Trimurti Institute
of Pharmacy Jalgaon,
Maharashtra, India

ABSTRACT

Capsule is most preferable dosage form. The capsule is made up of animal origin. The gelatin capsule shell may be soft or hard depending on their formulation. Despite the great advantages, of gelatin capsule but gelatin has a several drawbacks that limit its use for capsule. This review includes newer trends related to capsule shell. Such as capsule in capsule formulation, DUO-CAP. Polyherbal capsule. The non-gelatin capsule shell are made up of such as starch HPMC, PVA, Herbal medicine is the oldest form at health care known to mankind, the herbal formulation enhance physical endurance such as mental functions, non-specific resistance of the body.

INTRODUCTION

Capsule is most preferable dosage form. The word “Capsule” is derived from the Latin word “Capsula” which mean small box or container^[1] capsule are solid dosage forms in which drug is enclosed within either a hard or soft soluble container or “shell”.^[5] The gelatin capsule shell was invented early in the 19th century as a result of the need to mask the obnoxious taste of many medicinal substance such as oleoresin of copaiba. Which is extremely nauseating when taken by mouth.^[13] The capsule shell also polyherbal capsule. Herbal medicine is the oldest form of health care known to Mankind. In polyherbal preparation it will be very difficult if we want to estimate each and every ingredient in term of their chemical constituent. Herbal formulation enhances physical endurance, mental functions and non-specific resistance of the body and have been termed ‘s’ Adptogens various herbs like withania somnifera, Emblica officinalis. Asparagous racemosus, ocimum sanctum, piper longum are claimed to have immunomodulatory anabolic effect and the ability to improve vital energy.^[14] In the manufacture of pharmaceuticals, encapsulation refers to a range of technique used to enclose medicines in a relatively stable shell knows as a Capsule. The first patent was generated on 25th March 1834 for soft gelatin capsule to Mr.Francois Achille Barnabe Mothes a French pharmacy student. Hard gelatin capsule was invented by Jule cesarlehuby. Who was granted patent on 20th October 1846.^[13]

In pharmacy, capsule shell word has been described a glass ampoule and also as a name of protective cap over the stopper of a bottle of medicine.^[1]

Advantages of Capsule :-

- i) Capsule mask the taste and odor of unpleasant drugs can be easily administered.
- ii) They are easy to handle and carry.
- iii) They are quickly digested in the gastrointestinal track.^[1]
- iv) Capsule manufacturing requires fewer steps than tablet manufacturing.
- v) More possibilities for product identification.
- vi) Fewer development problems in capsules. Hence, allow quicker submission of a new drug for clinical trials.⁽¹³⁾
- vii) Reduce dosing frequency.
- viii) Improve patient compliance.
- ix) They are attractive in appearance.

- x) The shells can be specified (with titanium dioxide) or colored, to give protection from light.
- xi) They are slippery when moist and hence easy to swallow with a draught of water.⁽¹⁵⁾

Disadvantages of Capsules

- i) The concentrated solution which required previous dilution are unsuitable for capsules because if administered as such lead to irritation at the stomach.⁽¹⁾
- ii) HPMC shells are less resistant to indentation and have lower tensile strength than the gelatin shells which results in processing problems.⁽¹³⁾
- iii) High manufacturing cost.
- iv) The drugs which are hygroscopic absorb water from the capsule shell making it fragile and hence are inappropriate. For filling into capsule.⁽¹⁾
- v) Deliquescent materials cannot be incorporated. They may cause hardening or brittle capsule.
- vi) Highly sensitive Gelatin is extremely water soluble. Which helps it dissolve in the body. The downside is that soft gelatin capsules are very sensitive to heat and humidity in hot or humid climates soft gel caps may stick together or even break open before you have a chance to use them.⁽¹⁶⁾

Raw materials for Capsule Cover

The raw materials used in the manufacturing of both hard and soft gelatin capsules are similar, both hard and soft gelatin capsule shells contain gelatin, water, colorant and optional materials such as Preservatives and process aids.⁽¹⁾

Types of Capsules

A) Gelatin Capsules

- i) Gelatin capsules informally called gel caps or are composed of gelatin manufactured from the collagens of animal skin or bone. Gelatin derived from acid-catalyzed hydrolysis are referred to as type A and gelatin derived from the base catalyzed hydrolysis are referred to as 'B'.⁽¹⁻⁴⁾
- ii) Gelatin is not derivable from ungulate or liquid hooves which are composed of a different protein, keratin.⁽¹⁶⁾
- iii) Most gelatins used in the manufacturing of liquid-filled capsules have bloom strength at approximately 150-200 for soft gel and 220-280 for hard gels.⁽¹⁾

B) Vegetable Capsules

- i) Vegetable capsules are composed of hypermellos a polymer formulated cellulose. There are two types of capsule “hard and soft”. Capsules are available in many sizes to provide dosing flexibility.
- ii) Unpleasant drugs taste and odor can be masked by the tasteless gelatin shell.
- iii) Capsule are available in many sizes to provide dosing flexibility. Unpleasant drug taste and odor can be masked by the tasteless gelatin shell. ⁽¹⁶⁾
- iv) Hydroxy propyl methyl cellulose (HPMC) is mainly used in the manufacturing at such kind of capsule shell.
- v) Vegetable capsule shell is most commonly known as hypermellos.
- vi) Capsules are either hard (two piece) or soft (one piece) and are used to encapsulate pharmaceutical formulation.
- vii) Vegetable capsule are new approach which might be replacing the used at gelatin or non-vegetable capsule. ⁽¹⁵⁾
- viii) The administration of liquid and solid drug enclosed in hard gelatin capsules is one of the most frequently utilized dosage forms. ⁽⁵⁾

C) PolyherbalCapsule ⁽¹⁴⁾

- Herbal medicine is the oldest form of health care known to mankind. It is an integral part of the development of modern civilization.
- In poly-herbal preparations it will be very difficult if we want to estimate each and every ingredients in term of their chemical constituents. But if few major constituents having particular therapeutic action indicated in the labeled can be pinpointed then these constituents should be estimated quantitatively along with the other parameter through which presence at all ingredient can be confirmed.
- Herbal formulations enhances physical endurance,
 - (1) Mental Functions.
 - (2) Non-specific resistances at the body.
- The different plant materials are used in ply herbal capsule preparations.
- Fresh sample of four plants namely
 - (1) Withania Sannifera.
 - (2) Emblica Officinalis.
 - (3) Tinospora Cardifolia.

(4) *Eugenia Caryophyllus*.

- The plant was dried under shade to a constant weight and coarsely powdered in a electronic mixer, sieved through mesh number 40.

Storage

- i) Stored in air tight container.
- ii) Well closed container till further use.

Gelatin capsule shell

- Development of capsule shell by gelatin.
- Gelatin is very well-suited to this because it is an excellent film former and changes in liquid to solid at temperature just above ambient. ⁽¹⁹⁾
- Gelatin is the major component of the capsule and has been the material from which they have traditionally been made.
- The ability at the gelatin solution to get form a solid at a temperature just above ambient temperature conditions. ⁽⁵⁾
- The primary drawback in the use of gelatin is that it contains water which act as a plasticizer to a film. ⁽¹⁵⁾
- The reasons for it is that gelatin process the following basic properties.
 - (1) The gelatin films are homogenous in structure which gives them strength.
 - (2) It is readily soluble in biological fluids at body temperature.
 - (3) It is good film forming material producing a strong flexible film.
 - (4) It is non-toxic widely used in food stuffs and acceptable for use worldwide. ⁽⁵⁻¹²⁾
- The approximate amino acid composition at gelatin is glucine 21%, proline 12%, glutamic acid 10%, hydroxyproline 12%, alanine 9%, arginine 8%, aspartic acid 6%, lusine 4%, leucin 3%, serine 4%, valine 2%, phenylalanine 2%, threonine 2%, isoleufine 1%, hydroxylysine 1%, methionine and histadine<1% and tyrosine <0.5%. These values vary especially the minor constituents, depending on the sources of the raw material and processing techniques. ⁽¹⁾
- Capsules may be made from either type of gelatin, but mostly a mixture at both type is used considering availability and cost.
- Under the International Conference on Harmonization of technical condition for registration of Pharmaceutical for Human Use (ICH) condition for accelerated storage testing, gelatin undergoes a cross linkage reaction that reduces its solubility. ⁽¹⁴⁾

The newer trends related to capsule formulation

Capsule in-a capsule formation/formulation

Capsule in-a capsule formulation consist of two phase immediate and sustained phase. The immediate and sustained releasing does were found near about to be 3.24mg and 8mg respectively. ⁽¹⁹⁾

Application of capsule in a capsule formulation :- ⁽¹⁹⁻²¹⁾

- The technology is applicable for GI diseases like crohnis disease, GI cancers and acid reflux. It can even be used in case of diabetes.
- This technology is also used for the
 - (1) Ophthalmic.
 - (2) Optic.
 - (3) Rectal Ointments.
- Magnetic localization at chemotherapeutics at the site at GI tumors, which are simultaneously identifiable on X-RAY following intravenous administration of radio opaque contrast, would enable localized dosing while minimizing side effect associated with systemic administration.
- It is used for vaginal use and also rectal used.
- It can be quickly designed and complete a study in either a clinical or clinical setting.
- Duo cap can be used for immediate release or combined released for example solubilized prebiotics in the outer capsule and probiotics in the inner capsule.
- The outer capsule typically is used for immediate release at a combination product at first phase at a dual release formulation.

Drugs used for the preparation of DUO cap :-

1. Diazepam.
2. Digoxin.
3. Ibuprofen.
4. Penicillin G.
5. Phenytoin.
6. Furosemide.

Drug candidate for DUO cap

1. Digoxine – Drug which are having poor bioavailability.
2. Sulphanamide- Drug which requires large dose.

3. Penicillin- The drugs which having short half life.
4. Ibuprofen- Low melting point.
5. The drugs which having low dose or high potency.
6. Drugs which are having extensive plasma protein binding.



Fig. 1: DUO cap

Hard gelatin capsule:-

- They consist of a cylindrical body and cap both with hemispherical end and are usually made from gelatin and water with added preservative.⁽¹³⁾
- The majority of capsule product are made of hard gelatin capsule are made of hard gelatin capsules. Hard gelatin capsules are made up of two shells the capsule body and a shorter cap. The cap fits snugly. Over the open end at the capsule body.
- The basic hard gelatin capsules shell are made from mixture of gelatin sugar and water. They are clear, colorless and essentially tasteless.
- Humidity environment, hard gelatin capsule shell may lose their rigid shape and become distorted.
- In an opposite environment at extreme dryness, capsule may become too brittle and may crumbling during handling. Since moisture can be absorbed or released by the gelatin capsule. Capsule containing moisture-sensitive drugs are usually packaged in container.⁽⁵⁾

- Two piece capsules have been used for almost a century in the pharmaceutical field and the gelatin has been adopted as the characteristics as a gelatinizer. ⁽¹⁾
- Gelatin is a product which obtained from partial hydrolysis of collagens acquired from white connective tissue and skin.
- The gelatin is a one of the portion which is soluble in a warm water. ⁽⁵⁾

Table 1: Excipients of Hard gelatin capsule

Sr. No.	Excipients of Hard gelatin capsule
1.	Gelatin
2.	Preservatives (Methyl paraben, EDTA, Sodium benzoate, Propyl paraben)
3.	Colour
4.	Dyes and Pigments
5.	Opacifying agent
6.	Flavor and Fragrance

Size and modification in hard gelatin capsule :-

- Empty capsules ranging in size from 000 the largest to '5' the smallest.
- The hard gelatin capsule between 65mg to 9gm. ⁽¹⁾
- Achieve modified drug release.
- Modified the Advantages or Applications.
- Encapsulation at the various kind of the materials. ⁽¹³⁾

Soft gelatin capsule

- Soft gelatin capsules are prepared by adding a plasticizers, Such as glycerin or polyhydric alcohol (e.g. sorbitol) to gelatin.
- The plasticizer make gelatin elastic. ⁽¹⁾
- Soft gelatin (also called soft gel or soft elastic) capsules consist of one-piece hermitically-sealed soft shells.
- The soft gelatin capsules come in various shapes such as spherical elliptical, oblong and special tube shapes with and without twist off. ⁽¹⁶⁾
- The soft gelatin can contain non-aqueous liquids, suspension, pasty materials or dry powder.
- They are especially important to contain volatile drug substances or drug material susceptible to deterioration in the presence of air. ⁽¹⁾
- There are different type of process to manufacturing the soft gelatin capsules.

- Such as the plate process, the rotary die. process and reciprocating die process.
- Soft gelatin is subject to microbic decomposition when it becomes moist soft gelatin capsule may be prepared with preservatives to prevent the growth of fungi.
- Gelatin used for making soft capsules is usually of bone and skin origin and has 150-175g bloom strength.⁽⁵⁾

Important factors in soft gelatin capsules

- Polymorphism.
- Chemical Stability.
- Solubility
- Permeability
- Organic solubility
- Acceptable soft gel excipients:- fatty liquids PEGs propylene glycol surfactant.
- Drug excipients compatibility.

Table 2: Excipients of soft gels

Sr.No.	Excipients of gel
1.	Gelatin
2.	Dyes and Pigment
3.	Solvent
4.	pH-Adjusting additives
5.	Flavor and Fragrance
6.	Non Polar (Bee wax, Coconut oil, Triglycerin)
7.	Preservatives (Methyl paraben, propyl paraben, Sodium benzoate)
8.	Humectant (Polyol)

Advantages of soft gelatin:- (starch)⁽¹⁶⁾

- Good surface finish
- Coating at hard gelatin capsule with aqueous spray formulation can lead to softening of gelatin shell or gelatin shell may become brittle due to water evaporation and drying.
- Ready for fillings immediately following manufacturing.
- Offer greater resistance to humidity and heat than gelatin and allow easy filling as they non static.
- Soft gel are easy to swallow, one swallowed releases their contents very quickly.
- They may enhance the bioavailability of active ingredient.

Disadvantages

- Efflorescent material can not be incorporated, they may cause softening/leaching
- Water soluble material are difficult to incorporated.
- Deliquescent materials can not be incorporated. They may cause hardening or brittle capsule.
- Recent trends related to ⁽⁵⁾

1) Capsule shell

Manufacturing in capsule shell helps in improving physical strength and also enhance compatibility of fill material with capsule shell.

A) vegetarian capsule shell

Example:-

Hydroxy propyl methyl cellulose (HPMC)

Capsule HPMC has been approved ban Europe as an encapsulation material for organic product since December 2007.

Features:

1. Thermally and chemically stable.
 2. Less brittle even in low humidity (<1+ moisture content)
 3. Fast dissolution.
 4. Moisture content 4-6% less than gelatin capsule (15-16%)
- Starch capsule shell
 - The capsule suitable for enteric coating
 - Made from potato starch
 - Manufacturing by the injection molding techniques developed by capsule gel.
 - Polyvinyl alcohol PVL capsule
 - Less hygroscopic than gelatin capsule
 - Water soluble
 - Oxygen permeability through PVA copolymer with significantly capsule.

B) Animal origin capsule shell

a) Gelatin

- Available in gelatin 000 to 4
- They are good for moisture sensitive and hygroscopic.
- Odorless, tasteless, three year shelf life.

- When we added PEG it improves the mechanical strength.
- Moisture content between the 8-12% gelatin/PEG capsule gave equivalent mechanical strength to standard gelatin capsules with moisture between 13 to 16%.

b) Human gelatin

- Fibrogen and prodigen have announced calibrative work on high quality
- The high volume and low cost production of such recombinant human gelatin in maize

c) Fish gelatin

Features:

- Transparent capsule
- It contains from high quality, farm fish gelatinize a renewable resource.
- Excellent mechianability
- Some product like algae extract magnesium peptide and beta cotton are available in fish gelatin capsule.

CONCLUSION:

From the above study, the interest in using different type of capsule the hard gelatin capsule in developing in manufacturing medicines has increased considerably. This is most probably due to rapid advance in hard gelatin capsule doses forms. Two piece capsule have been used for almost a century and pharmaceutical field, and the gelatin has been adapted as the main material at these capsules due to its excellent characteristics as a gelatinizer. However gelatin is one as the protein derived from animals:, Therefore it is unstable form a chemical viewpoint and has a risk TES. The herbal formulation was formed with the help of four crude drugs viz. Withania, Somnifera, Tinospora, Cardifolia, Emblica Officinalis and Eugenia Caryophyllus and standardized as per the guidelines. Future prospect include the clinical trials at the finished product as the clinical efficacy is already proven in different animal studies. Capsule manufacturing will continue to improve the materials, processes and related technologies to this versatile dosage forms

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